Maternal T cells limit engraftment after in utero hematopoietic cell transplantation in mice.

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Public Summary:
With improvements in prenatal diagnosis and genetic testing, we can now diagnose a wide variety of congenital disorders that are amenable to stem cell based therapies. For example, many blood cell related and immunologic disorders can be potentially cured by stem transplantation. However, the current treatment of these disorders relies on postnatal bone marrow transplantation, which can carry significant morbidity. Treatment of these diseases in utero, prior to the maturation of the immune system, offers an innovative approach. With in utero stem cell transplantation, allogeneic (i.e. foreign) cells transplanted before the immune system matures may be perceived as "self," thereby avoiding a host immune response. However, levels of engraftment after in utero stem cell transplantation (IUSCTx) have been low in many animal models and clinically, this approach has only been successful in the setting of severe immunodeficiency. In this study we utilized a mouse model of IUSCTx to confirm previously published findings that the adaptive immune system impairs donor cell engraftment. Since the fetal immune system is relatively immature and cellular trafficking between a mother and her fetus is a well described phenomenon in human pregnancy, we hypothesized that maternal cells that travel into the fetus may pose the true barrier to donor cell engraftment. We demonstrated that there is a significant number of maternal immune cells in the blood of unmanipulated mouse fetuses, with significant increases in T cell trafficking after IUSCTx. Using genetically modified mice, we found that maternal T cells provided the main barrier to engraftment. In our experimental model, we also determined that genetically matching the donor cells to the mother resulted in high levels of engraftment. Our results indicate that supressing the maternal immune system may be a useful approach to improve donor cell engraftment, and that the clinical success of IUSCTx may be improved by transplanting cells harvested from (or HLA-matched to) the mother. Our research is currently focused on characterizing the maternal immune response to IUSCTx and understanding the mechanism by which donor cell rejection in the fetus occurs.

Scientific Abstract:
Transplantation of allogeneic stem cells into the early gestational fetus, a treatment termed in utero hematopoietic cell transplantation (IUHCTx), could potentially overcome the limitations of bone marrow transplants, including graft rejection and the chronic immunosuppression required to prevent rejection. However, clinical use of IUHCTx has been hampered by poor engraftment, possibly due to a host immune response against the graft. Since the fetal immune system is relatively immature, we hypothesized that maternal cells trafficking into the fetus may pose the true barrier to effective IUHCTx. Here, we have demonstrated that there is macrochimerism of maternal leukocytes in the blood of unmanipulated mouse fetuses, with substantial increases in T cell trafficking after IUHCTx. To determine the contribution of these maternal lymphocytes to rejection after IUHCTx, we bred T and/or B cell-deficient mothers to wild-type fathers and performed allogeneic IUHCTx into the immunocompetent fetuses. There was a marked improvement in engraftment if the mother lacked T cells but not B cells, indicating that maternal T cells are the main barrier to engraftment. Furthermore, when the graft was matched to the mother, there was no difference in engraftment between syngeneic and allogeneic fetal recipients. Our study suggests that the clinical success of IUHCTx may be improved by transplanting cells matched to the mother.